Human Metapneumovirus Circulation in the United States, 2008 to 2014


BACKGROUND: Human metapneumovirus (HMPV) infection causes respiratory illness, including bronchiolitis and pneumonia. However, national HMPV seasonality, as it compares with respiratory syncytial virus (RSV) and influenza seasonality patterns, has not been well described.

METHODS: Hospital and clinical laboratories reported weekly aggregates of specimens tested and positive detections for HMPV, RSV, and influenza to the National Respiratory and Enteric Virus Surveillance System from 2008 to 2014. A season was defined as consecutive weeks with \( \geq 3\% \) positivity for HMPV and \( \geq 10\% \) positivity for RSV and influenza during a surveillance year (June through July). For each virus, the season, onset, offset, duration, peak, and 6-season medians were calculated.

RESULTS: Among consistently reporting laboratories, 33,583 (3.6%) specimens were positive for HMPV, 281,581 (15.3%) for RSV, and 401,342 (18.2%) for influenza. Annually, 6 distinct HMPV seasons occurred from 2008 to 2014, with onsets ranging from November to February and offsets from April to July. Based on the 6-season medians, RSV, influenza, and HMPV onsets occurred sequentially and season durations were similar at 21 to 22 weeks. HMPV demonstrated a unique biennial pattern of early and late seasonal onsets. RSV seasons (onset, offset, peak) were most consistent and occurred before HMPV seasons. There were no consistent patterns between HMPV and influenza circulations.

CONCLUSIONS: HMPV circulation begins in winter and lasts until spring and demonstrates distinct seasons each year, with the onset beginning after that of RSV. HMPV, RSV, and influenza can circulate simultaneously during the respiratory season.

WHAT’S KNOWN ABOUT THIS SUBJECT: Human metapneumovirus is a respiratory virus that causes upper and lower respiratory infections. Clinical presentation, populations most severely impacted, and circulation patterns are similar to those of respiratory syncytial virus; however, national human metapneumovirus circulation has not been well described.

WHAT THIS STUDY ADDS: This study describes national human metapneumovirus circulation using laboratory detections reported to a national surveillance system from 2008 to 2014. Defining periods of elevated human metapneumovirus circulation may guide virus detection and clinical management, aiding in identifying illness and outbreaks.
First identified in 2001,1 human metapneumovirus (HMPV) is a cause of both upper and lower respiratory tract infections, including bronchiolitis and pneumonia, particularly among young children (<5 years), the elderly, and immunocompromised patients.2-5 Infection with HMPV has been associated with an estimated 20,000 U.S. hospitalizations annually among children aged <5 years.6 However, the infrequent testing and low index of suspicion associated with HMPV may have limited the assessment of temporal trends in HMPV circulation. Also, many studies have demonstrated that HMPV causes a respiratory tract infection clinically indistinguishable from infections caused by respiratory syncytial virus (RSV) and influenza.7-9 In contrast, the specific prevention options and some populations severely affected vary for HMPV, RSV, and influenza.7 Currently there is no vaccine for HMPV. Thus, describing HMPV circulation in the United States in the context of RSV and influenza may help clinicians to prioritize diagnostic testing, identify an etiologic agent, manage patients clinically, and choose appropriate prevention strategies.

Many studies have demonstrated a winter-to-spring circulation period for HMPV in temperate climates8-10 but determination of national HMPV trends and comparison of HMPV seasonality to RSV and influenza in multiple sites throughout the United States have not yet been done. A study conducted in 3 U.S. sites identified HMPV circulation in winter and spring months;6 however, it remains unclear if this pattern reflects trends in national HMPV circulation. The increased availability and use of molecular diagnostic assays to detect respiratory viruses11 in recent years has highlighted several HMPV-associated outbreaks throughout the United States12 and has enhanced the opportunity to evaluate national trends in HMPV circulation.

In the United States, surveillance for several respiratory viruses is conducted annually through the National Respiratory and Enteric Virus Surveillance System (NREVSS). In this study, we describe national HMPV circulation patterns and compare with patterns of RSV and influenza activity reported to NREVSS during 6 seasons from 2008 to 2014.

METHODS

NREVSS is a passive surveillance network established in 1984 that collects specimen test results for several respiratory viruses, including HMPV, RSV, and influenza. Approximately 300 clinical and public health laboratories in the United States report ≥1 specimen test result on average for 44 weeks in a surveillance year.13 Laboratories report weekly aggregates of the number of tests performed and positive detections by antigen detection, polymerase chain reaction (PCR), and viral isolation. The type of assay reported can vary depending on the respiratory virus and year. For RSV, we analyzed antigen detection reports; for influenza, we analyzed PCR reports; and for HMPV, we analyzed both antigen detection and PCR reports. The NREVSS surveillance year is defined as July of the starting year through the end of the following June to capture the typical national onset and offset of several respiratory viruses. Surveillance for RSV and influenza through NREVSS is well established and ongoing since 1984 and 1989, respectively. The first HMPV diagnostic test was reported to NREVSS in July 2005, but reports were insufficient for robust analysis until 2008 to 2009, when test reports to NREVSS exceeded 70,000.

Laboratories included in this analysis were selected based on annual duration and volume of reported test results. For RSV analysis, we included laboratories reporting ≥10 RSV antigen detection tests/week annually and ≥1 RSV antigen detection test for 30 of 52 weeks of the NREVSS year; for influenza analysis, we included laboratories reporting influenza by PCR to the World Health Organization collaborating laboratories;14 and for HMPV analysis, we included laboratories reporting ≥1 HMPV PCR or antigen detection test for 36 of 52 weeks of the NREVSS year. These are standard laboratory inclusion criteria for RSV and influenza; no standard inclusion criteria exist for HMPV.

For each virus, we calculated the weekly proportion-positive. To define the season for RSV13 and influenza,14 we used the widely accepted 10% weekly proportion-positive threshold. Specifically, the RSV or influenza seasons were defined as the first of 2 consecutive weeks when the proportion of positive weekly aggregates exceeded 10% positivity, and the season offset, as the last of 2 consecutive weeks when the proportion of weekly aggregates exceeded 10% positivity. To define the season for HMPV, we selected a 3% weekly proportion-positive threshold. We defined the HMPV season onset as the first of 2 consecutive weeks when the proportion of positive weekly aggregates exceeded 3% positivity, and the season offset, as the last of 2 consecutive weeks when the proportion of weekly aggregates exceeded 3% positivity. At a threshold of 3%, 84% to 94% of HMPV detections by antigen detection tests were captured each year, and 80% to 92% of HMPV detections by PCR tests were captured. For each virus, we calculated the onset, offset, peak, and duration (onset to offset) for each individual season and the median for the 6 seasons. A 4-season median rather than a 6-season median was calculated for influenza;
2 seasons (2008 to 2009, 2009 to 2010) were excluded because of the unprecedented occurrence of the H1N1 pandemic. An early season was defined as a season with an earlier onset than the 6-season median and higher peak proportion-positive than the 6-season median, and a late season was defined as a later onset than the 6-season median and lower peak proportion-positive than the 6-season median.

RESULTS

Among all laboratories reporting HMPV tests results to NREVSS from July 2008 to June 2014, 1 065 742 HMPV test results were reported and 38 160 (3.6%) were positive (25 409 [3.9%] by PCR; 12 751 [3.0%] by antigen detection). Among consistently reporting laboratories included in our analysis, 945 836 tests were reported from July 2008 to June 2014, and 33 583 (3.6%) were positive (21 972 [3.9%] by PCR, 11 611 [3.1%] by antigen detection) for HMPV, 1 839 877 tests were reported and 281 581 (15.3%) were positive for RSV, and 2 206 654 tests were reported (including specimens from the H1N1 influenza pandemic) and 401 342 (18.2%) were positive for influenza. During the study period, laboratories consistently reporting HMPV comprised general hospitals (60.3%), children’s hospitals/facilities (28.9%), public health facilities (9.6%), and reference laboratories (1.2%). The number of laboratories reporting HMPV tests increased from 21 laboratories representing 16 states in 2008 to 2009 to 60 laboratories representing 30 states in 2013 to 2014 (Table 1, Fig 1). The number of HMPV tests remained relatively constant over the 6 surveillance years, but the most prevalent diagnostic method reported fluctuated from year to year. In 2008 to 2009 and 2009 to 2010, 77% and 52%, respectively, of HMPV diagnostic tests reported were antigen detection; however, from 4 seasons that spanned 2010 to 2014, 52% to 85% of diagnostic tests reported were PCR. Similarly, the number of laboratories consistently reporting HMPV by antigen detection decreased from the 2008 to 2009 to 2013 to 2014 season median (median 21, range 15 to 25), and the number of laboratories reporting by PCR increased from the 2008 to 2009 to the 2013 to 2014 season median (median 34, range 9 to 49) (Table 1). Reporting both test methods for HMPV by laboratories was infrequent but increased from 3 in 2008 to 2009 to 9 in 2013 to 2014.

The weekly proportion of specimens positive by antigen detection or PCR methods for HMPV show definitive seasonal patterns each year (Fig 2A). The weekly proportion of positive HMPV tests ranged from a low of <1% between July and November to a maximum of 6% to 16% between March and April. We observed a slight biennial pattern with early and late seasons for HMPV based on the median weekly proportion-PCR positive tests with early (NREVSS surveillance years: 2009 to 2010, 2011 to 2012, and 2012 to 2013) and late (NREVSS surveillance years: 2008 to 2009, 2010 to 2011, and 2011 to 2012) seasons (Fig 2B).

Nationally, the HMPV 6-season median onset occurred in early January (week 1), and individual season onsets occurred from late November to late February within 5 weeks of the 6-season median
The HMPV season onset (Table 2). The HMPV 6-season median offset occurred in mid-May (week 20) ranging from late April to early July within 7 weeks of the individual season offsets. The 6-season median peak occurred in late March (week 12) and ranged from late February (week 7) to early May (week 17) for individual season peaks. The HMPV 6-season duration was 21 weeks (individual season duration range 19 to 25 weeks). Only minor variations in the occurrence of the HMPV season onset, peak, and offset were observed between PCR and antigen detection methods. The RSV seasons were most consistent, with very little change in onset, offset, and peak, unlike HMPV and influenza (Fig 3). The HMPV season onset, offset, and peak occurred after RSV for all 6 seasons. Year-to-year patterns in the sequential occurrence of offset and peak were similar among RSV and HMPV, but not influenza (Table 2). The 6-season median onset for RSV, influenza, and HMPV occurred in sequential order (Table 2). The first respiratory virus season median onset to occur was RSV, which had a 6-season median onset in early November (individual season onset range late October to late November). The influenza 4-season median onset occurred in early December.
(individual season onset range late November to early February). The HMPV 6-season median onset occurred in early January (individual season onset range late November to late February). The first respiratory virus season offset to occur was RSV. The 6-season median offset for RSV occurred in late March (individual season offset range mid-March to early April), followed by influenza in early May (individual season offset range early April to early June) and HMPV in mid-May (individual season offset range late April to early July). The 6-season median peak occurred in the following sequential order: RSV (late January, week 3), influenza (late January, week 3), and HMPV (late March, week 12). The 6-season median onset and peak for HMPV occurred 8 and 9 weeks, respectively, after RSV and 5 and 9 weeks after influenza, respectively (Table 2). The 6-season median duration for all 3 viruses were very similar at 21 to 22 weeks.

**DISCUSSION**

This is the first published summary of HMPV national data from NREVSS and demonstrates several unique features. From 2008 to 2014, the national HMPV data suggest that HMPV seasons occur later than RSV seasons, and based on the 6-season median onset, the RSV season occurred first, followed by influenza and then HMPV. The unprecedented H1N1 influenza pandemic that affected the 2008 to 2009 and 2009 to 2010 seasons made comparison during these seasons difficult to interpret. In addition, HMPV demonstrated a biennial pattern of early and late seasons. There were no distinct differences in HMPV seasonality determined by antigen detection and PCR, and PCR was the most prevalent diagnostic method used to identify HMPV in the last 4 years of analysis.

HMPV season durations occurred between November and July (6-season median 21 weeks). Weekly HMPV positivity fluctuated between nearly zero and ≥6% every 12 months, showing a distinguishable seasonal pattern. Similar to RSV and influenza, HMPV seasons occurred during winter and spring, as previously described.8–10 The weekly HMPV percent-positivity in this analysis never reached zero over the 6 years of surveillance, confirming previous reports of low but continuous HMPV circulation beyond winter and spring.15 We also observed a biennial pattern for HMPV of alternating early and late season from 2008 to 2014, which was not seen for RSV or influenza.16,17

The most prevalent HMPV diagnostic method reported shifted from antigen detection to PCR during 2008 to 2014. The shift toward increased reporting of PCR tests likely reflects changes in conventional diagnostic testing among participating NREVSS laboratories. Within any given season during this time period, a 3% weekly positivity measure captured ≥80% of PCR HMPV detections reported by qualifying institutions. The 3% weekly proportion is comparatively lower than the 10% positivity used to indicate elevated influenza and RSV circulations. However, as in other studies, we determined that a smaller proportion of diagnostic tests were positive for HMPV compared with other respiratory pathogens.18–21 The data analyzed were not robust enough to assess regional trends in HMPV circulation.

The cocirculation analysis suggest that HMPV, RSV, and influenza cocirculate, as previously described by Esper et al.15 Although the circulations of influenza, RSV, and HMPV overlap, the populations susceptible to severe infection and the management of these infections differ.22–24 Therefore, clinicians can use surveillance data, such as NREVSS, to help identify HMPV seasonality and help prioritize HMPV testing in patients with respiratory symptoms. As laboratory recruitment into NREVSS and PCR use continue to increase throughout the United States, future NREVSS data should be able to more reliably allow for more detailed analyses, including regional HMPV trends and outbreak occurrence, similar to those for RSV and influenza.

Our study had several limitations. Our findings are based on NREVSS, which is a passive and voluntary surveillance system in which (1)
participating laboratories can differ from season to season and may report different respiratory viruses; (2) HMPV test reporting is relatively new and does not garner the same test reporting volume or regional representation as more established respiratory viruses, such as RSV; (3) patient age and specific specimen information are not collected; and (4) duplication is a possibility if antigen detection and PCR testing are performed and reported on the same specimen or if >1 specimen is reported from a patient during the same illness episode. Because HMPV is a recently recognized respiratory virus, health professionals may not routinely consider or test for HMPV. Finally, we selected a low positivity threshold to define HMPV seasonality because fewer detections were positive for HMPV compared with other respiratory viruses monitored by NREVSS.

CONCLUSIONS
In the Unites States, HMPV circulates in distinct annual seasons with biennial patterns of early and late seasons. Our findings suggest that RSV onset occurs the earliest during the fall/winter respiratory virus season, followed by influenza and then HMPV. To distinguish HMPV from other cocirculating viruses, health professionals should consider HMPV testing during the respiratory season, especially when HMPV is the predominant virus circulating.

ABBREVIATIONS
HMPV: human metapneumovirus
NREVSS: National Respiratory and Enteric Virus Surveillance System
PCR: polymerase chain reaction
RSV: respiratory syncytial virus

REFERENCES


